COMPARATIVE EVALUATION OF EPIDURAL BUPIVACAINE WITH NEOSTIGMINE VERSUS EPIDURAL BUPIVACAINE ALONE IN LOWER ABDOMINAL SURGERIES FOR POSTOPERATIVE ANALGESIA

A study of 50 cases

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CERTIFICATE

This is to certify that the dissertation entitled **"COMPARATIVE EVALUATION OF EPIDURAL BUPIVACAINE WITH NEOSTIGMINE VERSUS EPIDURAL BUPIVACAINE ALONE IN LOWER ABDOMINAL SURGERIES FOR POSTOPERATIVE ANALGESIA ",** is a bonafide record work done by **Dr. J.SARVA VINOTHINI**, in the Department of Anaesthesiology, Government Rajaji Hospital, Madurai Medical College, Madurai.

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"No academic endeavor is single handedly accomplished.

This work is no exception"

It was with great trepidation and with a sense of unknown that I ventured into one of the novel and most advancing branches of Medicine Anaesthesiology. It is to the credit of my teachers that I managed to stay and began working on my dissertation.

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DECLARATION

I, Dr. J.SARVA VINOTHINI , solemnly declare that the dissertation titled "COMPARATIVE EVALUATION OF EPIDURAL BUPIVACAINE WITH NEOSTIGMINE VERSUS EPIDURAL BUPIVACAINE ALONE IN LOWER ABDOMINAL SURGERIES FOR POSTOPERATIVE ANALGESIA ", has been prepared by me.

This is submitted to The Tamilnadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment of the regulations for the award of MD degree Branch – X [Anaesthesiology].

Madurai. **Dr. J.SARVA VINOTHINI**
Date:

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INTRODUCTION

"For all the happiness that man can gain

is not in pleasure, but in rest from pain"

- John Dryden

Pain is the most frequent cause of suffering and disability. It is derived from the Latin word "peona" meaning "punishment" Pain is body's cry for help.

Pain is an extraordinary complex sensation which is difficult to define and equally difficult to measure in accurate objective manner. It is an unpleasant sensory and emotional experience, associated with actual or potential tissue damage or described in terms of such damage. Historically, the management of post-operative analgesia has always been plagued by lack of interest and enthusiasm among practitioners of anesthesia.

"…….. a visit to most post-operative wards will show the time honored ritual of inadequate post-operative pain management. Patients expect ineffective post-operative pain relief and their carers ensure that they are not disappointed ".

- Hammer M (Anesthesia 1991; 46:167-8)

Pain is a consistent and predominant complaint of most individuals following most surgical interventions. Failure to relieve pain is ethically and

morally unacceptable. Adequate pain relief could be considered a basic human right.

Adequate treatment of post-operative pain is essential not only from a humanitarian point of view, but also from a physiological aspect. Pain has several detrimental effects and good postoperative pain relief helps to decrease postoperative morbidity and hastens recovery. It also permits early ambulation and reduces the duration of hospital stay.

Poorly managed acute pain can lead to the occurrence of chronic pain. There is high incidence of pain following limb amputation, breast surgery, gall bladder surgery, lung surgery or inguinal hernia repair. The severity of post-operative pain following these surgeries is a potent predictor of subsequent chronic pain. Even today, despite many advances in drugs, devices and techniques for effective delivery of perioperative pain relief, poverty of interests in pain relief still continues, due to the hazards and fatal complications, that demand frequent visits by the physician, complex instruments that are needed to be set up and monitored.

Clearly, the need of the hour is modification of the anaesthetic technique itself, so that it provides postoperative analgesia as well.

An ideal postoperative pain relief technique,

- Should be effective in majority of patients receiving the technique,
- Should be simple, easy to administer and preferably a part of the

anesthetic technique,

- Should not lead to respiratory –depression,
- Should be free from motor paralysis and immobility.

In recent years, there has been a shift from the search for the more perfect analgesic, towards the use of more effective routes of administration and delivery system. This has led to the acceptance of Patient Controlled Analgesia & central drug administration.

Recently, many drugs like opioids and other adjuvants have been used in intrathecal and epidural space for post-operative pain relief. But, side effects like respiratory depression, pruritis, nausea and vomiting limits usage of opioids. There is also need for specialized monitoring and staffing which will increase the cost of health care.

So, many other drugs have been tried. There are around 25 neurotransmitters identified in the spinal cord. One among them is acetylcholine, which has been reported to exert antinociceptive effects.

Hence, the present study has been undertaken to combine neostigmine an anticholinesterase, which prevents breakdown of acetylcholine, along with bupivacaine for epidural administration to provide post-operative pain relief.

AIM OF THE STUDY

- To evaluate the efficacy of epidurally administered Neostigmine, along with Bupivacaine for post-operative pain relief in lower abdominal -surgeries.
- To evaluate the merits and demerits of Neostigmine administered epidurally.

ANATOMY OF EPIDURAL SPACE

It is a potential negative space within the cranium. The endosteal and meningeal layers of duramater are closely united, but below the foramen magnum the two layers separate, the outer layer becoming the periosteal lining of spinal canal and inner layer, the spinal dura mater. Between the two layers lies the epidural space.

The spinal canal is triangular in cross section. The Epidural space is widest in the midline posteriorly in the lumbar region, averaging about 5mm. In mid thoracic region the distance is 3-5 mm in midline.

BOUNDARIES OF EPIDURAL SPACE:

Above: The foramen magnum where the periosteal and the spinal layers of duramater fuse together.

Below: The sacrococygeal membrane

Anteriorly: The posterior longitudinal ligament covering the posterior aspect of vertebral bodies and the intervertebral discs.

Laterally: Pedicles of the vertebra and the intervertebral foramina.

Ligamentum flavum is an important landmark for technical identification of the epidural space. It is composed of yellow elastic fibres disposed in a vertical direction. It connects the upper and lower borders of adjacent lamina. It

is thinnest in the cervical region, becoming progressively thicker lower down the spine and thickest in the lumbar region.

CONTENTS OF EPIDURAL SPACE:

1. Dural sac
2. Spinal nerve roots
3. Epidural plexus of veins
4. Spinal arteries
5. Lymphatics
6. Fat

31 pairs of spinal nerves with their dural cuff traverse the space on their way to intervertebral foramina.

The internal vertebral venous plexus draining both cord and canal lies mainly, in the anterolateral parts of epidural space. These veins have no valves – VALVELESS, VERTICAL, VERTEBRAL VEINS OF BATSON. It has segmental connections at all levels. Through this network, increased intra-abdominal and intrathoracic pressures are transmitted to epidural space and the epidural veins get distended. They connect pelvic veins below to the intracranial veins above.

The contents of epidural space lie cushioned in a packing of semi-fluid

lobulated fat. The epidural fat constitutes an important pharmacologic space and depot for injected local anaesthetic agents. It is one of the three competitors for the drugs, other two being central nervous tissue (spinal cord and spinal roots) and blood vessels. Drugs with high lipid solubility and lipoprotein binding characteristics will tend to enter the fat phase and remain there for periods of time, depending on their pharmacodynamics and on the briskness of local blood flow competing for uptake.

The volume of the extradural space is large, compared to the intradural volume. Usual distance between skin and extradural space is 4- 5 cm. This epidural space can be entered posteriorly at any level of spinal column and depending upon the level where it is entered, it is called cervical, thoracic, lumbar or sacral epidural.

EPIDURAL PRESSURE:

There are many theories for the presence of negative pressure in epidural space: -

1. **Cone theory: (Eaton – Lawerence)**

   Dimpling of dura by needle: The advancing needle dents a cone of resilient dura within the unyielding walls of spinal canal.

2. **Transmission theory: (Mc Intosh – Bryce smith)**

Transmission of negative pressure from thorax via paravertebral spaces especially in thoracic region

3. Full flexion of back
4. Initial bulge forwards of the yellow ligament in front of the advancing needle, followed by its rapid return to the resting position once needle has perforated the ligament.
5. Redistribution of CSF in the intradural space greater in recumbent position, than in vertical position.

Negative pressure in the extradural space is not the same at all levels and in the sacral canal it is absent. It is readily recorded in the cervical and thoracic regions when patients were sitting up, but less marked in lumbar region. Better negative pressure was obtained in the lumbar region when patients were sitting up in a flexed position, for the abdominal contents are more compressed. The intra-abdominal pressure is higher in the sitting position and this pressure is transmitted to the lumbar epidural space.

IDENTIFICATION OF EPIDURAL SPACE

Techniques for identification of the epidural space:

1. Sudden lack of resistance to the advancing needle as it leaves the dense ligamentum flavum (Pages).
2. Sudden ease of injection of little air or liquid, from a freely running syringe attached to the needle (Sicard, Forestier, Dogliotti)
3. Withdrawal of hanging drop of saline in the hub of needle (Gutierrez sign)
4. In an unconscious patient, rapid injection of liquid into the extradural space is accompanied by increase in rate & depth of respiration (Durran's sign)
5. Injection of distilled water will cause some discomfort to the patient, if placed in epidural space (Lund sign).

Visual aids:

1. Movement of bubble on odom's indicator
2. McIntosh extradural space indicator
3. McIntosh spring loaded syringe
4. U tube manometer
5. Aneroid manometer

6. Zorraquins bulb indicator
7. Zelenka balloon indicator
8. Brooks indicator
9. Dawkin’s gravity indicator
10. Auditory devices – sagarnaya
11. Ultrasonic localization

PHYSIOLOGY OF PAIN

In 1979, the International Association for the Study of Pain (IASP) proposed a definition of pain as, “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage”.

Surgery produces local tissue damage with consequent release of algesic substances (prostaglandins, histamine, serotonin, bradykinin, 5-hydroxytryptamine and substance-P) and generation of noxious stimuli, that are transduced by noiciceptors and transmitted by Aδ and C nerve fibres to the neuraxis. Further transmission is determined by complex modulating influences in the spinal cord. Some impulses pass to the anterior and anterolateral horns, to provoke segmental reflex responses. Others are transmitted to higher centres, via the spinothalamic and spinoreticular tracts, where they produce suprasegmental and cortical responses.

Cortical responses in awake, unanaesthetised patients after surgery are provoked by nociceptive impulses reaching the highest brain center, where complex systems concerned with integration and perception of pain are activated. Apprehension and anxiety may accompany pain resulting in additional hypothalamic stimulation.

There are 2 components of pain – neurophysiologically mediated sensory

component and an emotional experience.

There are 2 types of pain:

1. **Physiological pain** is a transient sensation due to noxious, mechanical, thermal, chemical stimulus each with a clearly defined threshold and without causing damage to the nervous system.
2. **Pathological pain** is an inflammatory response to tissue injury or damage to central nervous system with an alteration in perception. Pain following surgery is pathological.

There are 2 major theories of pain:

1. **Specific theory** – proposed by Von Frey states that the pain is due to stimulation of specific receptors.
2. **Intensive summation pattern theory** – proposed by Gold Scheider states that there are no specific pain receptors and any sensory stimulus if sufficiently severe would produce pain.

ORGANISATION OF PAIN PATHWAYS

According to the recent theory, pain pathway is organized as follows:

RECEPTORS: -

Nociceptive receptors are fine, profusely branched, free nerve endings covered by schwann cells with, little or no myelin. They are present in skin, viscera and other organs.

The various nociceptors are

1. Cutaneous nociceptors

They are connected to small myelinated Aδ fibres with conduction velocities between 5 to 30 metres / second. They form free nerve endings in the superficial layer of the dermis with terminations that penetrate in the epidermis. These receptors respond particularly well to pinching or squeezing the skin or to pinprick. Cutaneous nociceptors are also connected to unmyelinated C afferent fibres with conduction velocities 1.5 meters/second or less. They respond to noxious levels of mechanical, thermal or chemical stimuli. In addition, they are sensitive to many pain producing substances such as bradykinin, capsaicin, potassium ions, histamine, acetylcholine and strong acids. So they are known as polymodal nociceptors or C-fibres mechano-heat (CMH) nociceptors.

2. Muscle and joint nociceptors

Nociceptors are also described in deep tissues such as muscles, ligaments and joints.

Aδ afferent fibres – respond to chemicals known to cause muscle pain such potassium ions, bradykinin or serotonin and to sustained contraction of the muscle.

C – fibres –respond to noxious chemicals and to other noxious stimuli,

that produce muscle pain such as, pressure or heat and also muscle pain due to contraction under ischemia.

3. Visceral nociceptors

They are thought to play a role in signaling of events such as myocardial ischemia, irritation of airways, pulmonary congestion, testicular injury, biliary and renal colic or labour pain. Most of these are connected to unmyelinated C afferent fibres.

FIRST ORDER NEURONS: -

Pain signals are transmitted from pain receptors along myelinated A-delta fibres and unmyelinated C fibres and terminate on cells in the dorsal horn. Anatomically A-delta fibres synapse with cells in laminae I and V (wide dynamic neurons) of the dorsal horn, whereas C fibres synapse with cells in laminae II and III, which are also known as the substantial gelatinosa.

SECOND ORDER NEURONS: -

Cells in laminae I and V of spinal cord are spinothalamic cells, and about 75% of fibres originating from these cells cross to the contralateral spinothalamic tract.

Near the thalamus, the spinothalamic tract divides into a lateral portion often called the neospinothalamic tract, and a medial portion called the paleospinothalamic tract.

The phylogenetically newer portion of the spinothalamic tract

(neospinothalamic tract) projects to the posterior portions of the thalamus and is considered to be involved in the spatial and temporal aspects of pain perception.

The phylogenetically older portion of the spinothalamic tract (paleospinothalamic tract) projects to the medial thalamus and is responsible for the initiation of unpleasant aspects of pain as well as autonomic responses to pain. The paleospinothalamic tract has numerous synapses with the reticular formation of the brain stem, the medial thalamus, the periaqueductal gray matter, and the hypothalamus.

Other pathways involved in cephalad transmission of pain impulses include the spinocervical tracts, spinoreticular tracts and spinomesenencephalic tracts.

THALAMIC TERMINUS: -

Most of the fibres of the spinothalamic tract terminate in the nucleus ventroposterolateralis (VPL), which is the major sensory relay nucleus. The other fibres terminate in the posterior group of nuclei that include nucleus venteroposteromedialis, intralaminar nuclei, ventrobasal complex, and hypothalamic nuclei.

THIRD ORDER NEURONS: -

Projections from the thalamus end in three cortical areas, SI II and the cingulate gyrus on the side opposite to the stimulus. The cingulate gyrus is

involved in emotion. C fibres transmit burning and aching types of pain, which is consistent with the diffuse projections of these fibres from the thalamus into the limbic and subcortical areas. These signals also activate reticular activating system.

Some descending neural pathways exert a modifying effect on incoming noxious input. That, such sites existed was predicted by the gate control theory of pain. Many such sites, such as the periaqueductal gray matter, have high concentrations of endogenous opioid neurotransmitters. These areas project to the rostroventral medulla and, via the reticulospinal tracts and the dorsal lateral funiculus, to laminae I, II and V. Other neurochemicals like norepinephrine and serotonin are implicated in these inhibitory or modulatory circuits.

PERCEPTION OF PAIN

The threshold of perception of pain is, the lowest intensity of stimulus recognized as pain. The conscious awareness or perception of pain occurs when the thalamocortical pathway is destroyed. Somatosensory cortex is essential for the accurate localization, appreciation of intensity and other discriminative aspects of pain. Prefrontal cortex sub serves the unpleasant affective and emotional reaction to pain.

Gate control theory of pain

Melzack and Wall proposed the gate control theory in 1965. Dorsal horn of the spinal cord may function as a gate, controlling the subsequent transmission of impulses via the spinothalamic tract. The stimulation of large

diameter afferent fibres from an area in which pain is initiated inhibits smaller pain fibres and reduces pain. The mechanism may be presynaptic inhibition at the endings of the primary afferents that transmit pain impulses.

Modulation of pain transmission via the spinothalamic tract through the stimulation of large afferent fibres, excite the inhibitory cells in the lamina II and III of dorsal horn, which in turn causes pre and post synaptic inhibition of secondary transmission neurons (T cells) in the lamina V of dorsal horn and interrupt pain pathway. Conversely, stimulation of small pain afferents (C fibres) inhibits the T cells in the excitatory state, thus facilitating transmission of pain.

MODULATION OF PAIN

Pain impulses traveling via afferent nerves from pain receptors enter the dorsal horn of the spinal cord and at this site, release excitatory neurotransmitters, such as glutamate or a 11-aminoacid peptide known as substance P. These are necessary for further cephalad transmission of pain. Transmission of pain impulse may be modulated by, activation of descending inhibitory pain pathways that pass from brain to the spinal cord. It seems likely that a central nervous system substance, possibly endorphins is responsible for activating these descending inhibitory pathways. Opioid receptors in the substantia gelatinosa of the spinal cord probably have substance P containing terminals and opioids produce analgesia by inhibiting release of substance P.

Furthermore opioid binding sites and endorphins are present in the periaqueductal gray area of the midbrain, where electrical stimulation can produce analgesia. Thus endorphins and their receptors are well situated to function in an endogenous pain suppression system. In addition to endorphins, other nonopioid inhibitory neurotransmitters released by descending pathway fibres may include serotonin, noepinephrine, and possibly glycine and gamma-aminobutyric acid.

Central sensitization or wind up

Prolonged nociceptive stimulation leads to hyperexcitability of dorsal horn cells and increased cephalad transmission resulting in increased pain sensation. This is responsible for chronic pain syndromes.

Descending inhibitory pathways and endogenous pain control mechanisms

It extends from the hypothalamus along the periventricular and periaqueductal grey matter, which communicate through dorsolateral funiculus to end in the nucleus raphe magnus and locus ceruleus. Stimulation anywhere along this tract, releases endogenous opioid like peptides and endorphins, which activate serotoninergic pathway via descending reticulobulbar spinal system, interact with lamina I and II of the dorsal horn and exert analgesia. Another descending inhibitory pathway arises from locus ceruleus in pons and projects directly to the spinal cord. Here, neurotransmitter is noradrenaline and this

pathway inhibits pain responses in spinal cord by, α2 adrenergic mechanism.

RECENT CONCEPTS: -

Spinal cholinergic anti-nociception

GABAergic interneurones posses muscarinic receptors on both axon terminals and somatodendritic sites, that the activation of these receptors increases the excitability of inhibitory interneurones and enhances GABA release in the substantia gelatinosa. This GABAergic inhibitory system is further controlled by cholinergic neurons located in the deep dorsal horn. Those effects may be responsible for the antinociceptive action produced by the intrathecal administration of muscarinic agonists and acetylcholinesterase inhibitors.

Studies conducted have shown that spinally mediated cholinergic antinociceptive response was mediated through, inhibition of the local release of substance P. The results of those studies support the role of endogenous spinal acetylcholine, in pain modification and suggest an interaction with substance P neurons of the dorsal spinal cord.

α2 adrenergic agonists like clonidine are thought to produce analgesia, in part, by activating spinal acetylcholine release.

Spinal cholinergic pathways for antinociception may interact with spinal opioid and adrenergic nerve tracts. There is now substantial evidence that acetyl

cholinesterase inhibitors and muscarinic receptor agonists increase the pain threshold after spinal administration. A muscarinic interneuron may explain the interactions with other neurotransmitters.

Muscarinic receptors are concentrated in the superficial layers of the dorsal horn of the spinal cord, an area of noxious sensory processing and these reflect innervation, primarily from cholinergic neurons with cell bodies deep in the neck of dorsal horn. Spinal injection of cholinergic agonists results in analgesia that primarily reflects muscarinic receptor activation.

Nature of postoperative pain

After surgery, the patient may complain of pain directly related to the site of surgery or coincidentally from other sites. Noxious stimulation, which may give rise to pain, can be classified as:

- **Mechanical:** Direct trauma to tissues, wound tension, muscle spasm, distension of a viscus
- **Chemical:** Inflammation, tissue ischemia
- **Thermal**
- **Radiation**

The site of surgery is an important factor in determining the degree of pain, its localisation and duration. Operations, which invade the superficial tegument (the skin) but do not divide major somatic muscle groups, cause a type of pain described as soreness and dullache, both very sensitive to low

concentrations of analgesics.

Muscle splitting laparotomy approach causes, less postoperative pain than the muscle dividing approach. Any laparotomy, which involves the cutting of muscle and tendinous layers, is associated with pain, which is exaggerated by movement especially, deep breathing and coughing. It is less amenable to treatment with opioids than the poorly localized, dull aching pain characteristic of invasion of the peritoneum.

Most postoperative pain is related to muscle spasm, which is a defence mechanism to minimize movement or distortion of the injured part. Relief of muscle spasm by low concentrations of local anaesthetics can be surprisingly effective in relieving pain.

Psychological aspects of pain

The preexisting psychological state of a patient may have a strong influence on the central processing component of acute pain after surgery. The same operation can elicit very different responses from patients, some of who will decline analgesia because they do not feel that it is necessary, whereas others may find it impossible to achieve adequate analgesia.

Physiological effects of postoperative pain

Sympathoadrenal outflow

Increase in plasma catecholamines may result in dysrhythmias,

tachycardia and hypertension, which may induce myocardial ischemia in susceptible patients, because of increased myocardial oxygen demand or reduced supply.

Blood coagulation

Pain activates the coagulation system, platelet aggregation and alters the fibrinolytic system. These alterations serve to enhance clotting and may lead to postoperative complications such as, deep venous thrombosis, pulmonary embolism and arterial thrombotic events.

Neuroendocrine stress response

Increased release of cortisol, aldosterone and ADH, during peri-operative period may contribute to postoperative hyperglycemia, oliguria and water retention. ACTH, glucagons, renin and angiotensin II are the other hormones that are increased after postoperative pain perception.

Pulmonary dysfunction

Pulmonary dysfunction is noted most commonly, after upper abdominal and thoracic operations. Loss of lung volumes due to acute restrictive pulmonary dysfunction (thoracic splinting) may result in relative hypoxemia, major atelectasis and pulmonary consolidation.

Gastrointestinal effects

Sympathetic hyperactivity related to pain can cause reflex inhibition of gastrointestinal function and leads to paralytic ileus, nausea, vomiting and urinary retention.

Advantages of epidural analgesia in the postoperative pain relief

1. Reduced sympathoadrenal outflow
2. Reduced neuroendocrine responses
3. Reduced incidence of deep venous thrombosis and pulmonary embolism as well as arterial thrombotic events (may be related to an inhibitory effect on platelet aggregation as well as improvement in lower limb blood flow).
4. Improved postoperative pulmonary function may be due to early ambulation, improved cough reflex and desplinting of the thorax.

PHARMACOLOGY OF BUPIVACAINE

Bupivacaine was synthesized by Bo af Ekenstem in 1957. Telivuo introduced it for clinical use in 1963. At present, bupivacaine is acknowledged as most suitable agent for epidural and intrathecal administration.

Chemistry

It is an aminoamide type local anaesthetic. It is N- butyl pipecolic 2,6 dimethyl xylidide hydrochloride. The aromatic ring system gives it a lipophilic character. The base is not soluble, but the hydrochloride salt readily dissolves in water. It is very stable both to repeated autoclaving and to acids and alkalis, but solutions containing adrenaline should not be autoclaved more than twice. Commercial bupivacaine is a racemic mixture of both isomers.

Molecular weight	-	324 Daltons
Pka	-	8.05
Protonation at pH of 7.4	-	80%
Protein binding	-	95%
Volume of distribution	-	72 litres
t½ (∝)	-	2.7 mins
t½ (ß)	-	2.8 mins
t½ (γ)	-	3.5 hours

Clearance - 0.47 litres/min

PHARMACOKINETICS

Absorption:

Systemic absorption of injected local anaesthetic is, modified by several factors, including the site of injection, dosage and volume, addition of vasoconstrictors and pharmacologic profile of the agent itself. Neuronal uptake of the drug is presumably enhanced by higher local drug concentration Toxic blood concentration not definitely established but approximately 1.5 - 3μg/ml

Distribution:

A two-compartment model can describe the systemic distribution of local anaesthetics. The rapid disappearance phase is due to uptake by rapidly equilibrating tissues (i.e tissues that have high vascular perfusion). The slower phase of disappearance from blood is a function of particular compound.

Metabolism and excretion:

Metabolized in the liver by N-dealkylation. The metabolic breakdown product pipecolylxylidine, is approximately one-eight as toxic as bupivacaine. Pipecolylxylidine and unchanged bupivacaine are slowly excreted in about equal proportions in urine.

Use of Vasoconstrictors:

Addition of adrenaline does not greatly prolong its effect but reduces its toxicity. Peak effects of bupivacaine, are minimally influenced by the addition

of a vasoconstrictor, after injection into the lumbar epidural space, but significantly reduces the rate of vascular absorption of this drug, when used for peripheral nerve blockade.

PHARMACODYNAMICS: -

Mechanism of action:

Local anesthetics prevent transmission of nerve impulses (conduction blockade) by, inhibiting passage of sodium ions through ion selective sodium channels in nerve membranes. When progressively increasing concentrations of local anaesthetic, are applied to a nerve fibre, the threshold for excitation increases, impulse conduction slows, the rate of rise of action potential declines, the action potential amplitude decreases and finally the ability to generate an action potential is abolished.

Action on nerves:

Different types of nerve fibres differ significantly in their susceptibility to local anaesthetic blockade, on the basis of size and myelination. Upon application of a local anaesthetic to a nerve root, the smaller B (<3 μm) and C (0.3-1.2 μm, unnmyelinated) type fibres are blocked first. The small Aδ fibres (2-5μm) are blocked next. Thus pain fibres are blocked first, other sensations disappear next and motor function is blocked last.

Effect of fibre diameter

Local anaesthetics preferentially block small fibres because; the distance over which such fibres can passively propagate an electrical impulse (related to the space constant) is shorter. The local anaesthetic, to halt impulse propagation, must block three successive Nodes of Ranvier in a myelinated fibre. Myelinated nerves tend to become blocked before unmyelinated nerves of the same diameter. For this reason, the preganglionic B fibres may be blocked before the smaller unmyelinated C fibres.

Effect of firing frequency:

Blockade by local anaesthetics is more marked at, higher frequencies of depolarization and with longer depolarization. Sensory fibres especially, pain fibres (Aδ and C fibres) have a high firing rate and a relatively long action potential duration (up to 5 ms). Motor fibres fire at a slower rate and have a shorter action potential duration (<0.5ms). Aδ and C fibres are smaller diameter fibres that participate in high frequency pain transmission. They therefore are blocked sooner with low concentration of local anaesthetic, than are the A∝ fibres.

SIDE EFFECTS:

1. Allergic reactions:

Allergic reactions are rare despite, the frequent use of these drugs. An allergic reaction may also be due to methylparaben or similar substances used as preservatives in commercial preparation.

2. Systemic toxicity:

Systemic reactions to local anaesthetics primarily involve the central nervous system and the cardiovascular system. This is due to excess plasma concentration of the drug.

a. Central Nervous system toxicity

The initial symptoms of local anaesthetic induced CNS toxicity are feelings of lightheadedness and dizziness, followed frequently by visual and auditory disturbances like difficulty in focusing and tinnitus. Objective signs of CNS toxicity are usually excitatory and include shivering, muscle twitching and tremors initially involving, muscles of the face and distal parts of the extremities. Ultimately, generalized convulsions of a tonic-clonic nature occur. In some patients, CNS depression without a preceding excitatory phase is seen particularly if other CNS depressant drugs have been administered.

b. Cardiovascular system toxicity:

Bupivacaine depresses the rapid phase of depolarization (Vmax) in purkinje fibres and ventricular muscles to a greater extent than, Lidocaine does.

Rate of recovery from a use-dependent block is also slower. So, there is incomplete restoration of Na^+ channel availability between action potentials, particularly at high rates, leading to arrythmogenicity.

High blood levels prolong conduction time through various parts of the heart. Extremely high concentrations also depress spontaneous pacemaker activity resulting in sinus bradycardia and arrest. There is also a dose-dependent negative ionotropic action. The CC/CNS dose ratio for bupivacaine 3.7 ± 0.5

Treatment

No medications are uniformly effective in facilitating resuscitation from bupivacaine induced cardiac arrest or severe ventricular tachycardia. Basic principles of securing the airway, providing oxygenation and ventilation and instituting chest compression, should be emphasized. Epinephrine, bretylium, amrinone and phenytoin have been tried.

Uptake of epidural bupivacaine into the cerebrospinal fluid is 30.6µg/ml, 90minutes after epidural injection of 150ml (30 ml of 0.5% solution) with, 1 in 2,00,000 epinephrine. CSF concentration of this order (0.03 mg/ml) is relatively low, compared to the levels of other agents found in CSF after epidural injection. Very high lipid solubility and protein affinity of bupivacaine suggest that, a considerable portion of the drug will distribute itself rapidly out of CSF phase into the neuraxis and the CSF concentration will not necessarily reflect the actual degree of neural uptake that is taking place.

Clinically efficacy of bupivacaine is little affected by presence or absence of adrenaline

But, differences do occur in the quality of blockade and vascular uptake. So, epinephrine is clearly advantageous. Marked increases in blood levels of bupivacaine have been observed, when epinephrine is omitted.

As with all local anaesthetics, ideal practice should avoid solutions of low pH premixed with epinephrine and instead, epinephrine should be added freshly in accurately measured amounts to produce a concentration of 5μg/ml, just prior to use. In this way, pH is usually several units more alkaline than premixed solutions and therefore, more likely to have faster onset from the greater proportion of nonionized lipid soluble base.

EPIDURAL BUPIVACAINE: -

Bupivacaine is extensively used for lumbar epidural blockade particularly, when prolonged analgesia is required. It is reputed to be four times as potent as lignocaine, so that 0.5% bupivacaine solution is roughly equivalent to 2% lignocaine.

For single shot epidural, the maximum safe dose is about 2mg/kg. Analgesia in postoperative period lasts for 3-5 hours. Onset is within 10-20 minutes when, 0.25% - 0.75% solution used.

For prolonged analgesia 50mg doses can be repeated every 2-3 hours, a

maximum dose without adrenaline of 320 mg and with adrenaline of 500 mg could be given with safety. Clinically occurring blood levels of bupivacaine are usually; well below those likely to produce toxic symptoms and it is a less cumulative drug than lignocaine or mepivacaine.

CLINICAL PREPARATIONS:

Bupivacaine is manufactured in concentrations of 0.25% and 0.5% for epidural use.

0.5% Bupivacaine

This was the strength originally selected for surgical anaesthesia and the drug performs reasonably well in this concentration. Latency is similar to 0.5% tetracaine. **Latency of onset is 5.8 minutes – 18.2 minutes.**

Dose requirements decline form about 6.75mg per segment at 20yrs to 3.8mg per segment at 80years; average at 40years 5.8mg per segment.

Quality of motor blockade is relatively less when compared to, effective sensory analgesia. However, intensity of sensory block in L5 and S1 is unimpressive and quality of analgesia in these segments is not usually sufficient for comfort, during operations on lower leg and ankle in conscious patients.

2-segment regression time is 196 ± 31 minutes with 1/2,00,000 epinephrine.

0.25% Bupivacaine

Latency is slow, motor block negligible and quality of surgical anaesthesia in adults is barely adequate for satisfactory operating conditions. However, this dilute solution with epinephrine is ideally suited for relief of pain in labour and for postoperative pain relief.

0.125% Bupivacaine

Used mainly for labour analgesia.

Uses of Bupivacaine:-

1. Local infiltration
2. Peripheral nerve blocks
3. Spinal anaesthesia
4. Epidural anaesthesia
5. Labour analgesia

PHARMACOLOGY OF NEOSTIGMINE

The action of acetylcholine released from autonomic and somatic motor nerves are terminated by enzyme destruction of the molecule. Hydrolysis is accomplished by the action of acetylcholinesterase, a protein with a molecular weight of about 3,20,000 Daltons, which is present in high concentrations in the cholinergic synapses.

Neostigmine is an anticholinesterase most often administered by the anaesthesiologists, to facilitate the speed of recovery from the skeletal muscle effects produced by non-depolarising muscle relaxants.

MECHANISM OF ACTION

Enzyme inhibition

Neostigmine inhibits the breakdown of acetylcholine by virtue of it being hydrolyzed by acetylcholinesterase, indirectly increasing the amount of acetylcholine available to compete with the nondepolarizing agent, thereby re-establishing neuromuscular transmission. In this process, acetylcholinesterase is carbamylated, and it cannot hydrolyze acetylcholine. Carbamylated acetylcholinesterase has a halftime of 15-30 minutes. The clinical duration of cholinesterase inhibitor effect however is probably most influenced by the rate of drug disappearance from the plasma. Difference in duration of action can be

overcome by dosage adjustments.

In the absence of nondepolarizing neuromuscular blocking drugs, administration of an anticholinesterase drug may produce spontaneous contractions (fasciculations) of skeletal muscles. These presynaptic effects are abolished by a small dose of nondepolarizing neuromuscular blocking drug, suggesting that acetylcholine receptors are involved.

Direct effects at neuromuscular junction

If dose greater than that administered clinically, anticholinesterase drugs produce neuromuscular blockade probably due to an excess of acetylcholine be resulting in desensitization (endplate no longer responsive to acetylcholine).

Physical structure

Neostigmine is a quarternary ammonium derivative of physostigmine. The carbamate moiety provides covalent bonding to acetylcholinesterase. The quarternary ammonium group renders the molecule lipid insoluble so that it cannot pass through the blood brain barrier.

PHARMACOKINETICS

After a single bolus dose, the plasma concentration of neostigmine reaches a peak and decreases rapidly during the first 5-10 minutes. The volume of distribution is 0.7 to 1.4 liters/kg, and the elimination half time is 77 minutes. The clearance is 9.2ml/kg/min, which is much greater than the glomerular

filtration rate.

Neostigmine does not penetrate lipid cell membrane layers such as the gastrointestinal tract or blood brain barrier.

Neostigmine has an onset of action of 7-11 minutes. The duration of action of anticholinesterase drugs is governed largely by the rate of disappearance of these drugs from the plasma. For example, the half time of the carbamylated enzyme (15-30 minutes) is much shorter than the elimination half times of the anticholinesterase drugs (60-120minutes).

Renal clearance

Anticholinesterase drugs are actively secreted into the lumens of the renal tubules. Renal clearance accounts for approximately 50% of the elimination of neostigmine. As a result, the elimination halftime is greatly prolonged by renal failure.

Metabolism

Mainly metabolized in kidney. The principal metabolite of neostigmine is 3-hydroxyphenyl trimethylammonium, which has approximately one-tenth of the antagonistic activity of the parent compound.

PHARMACODYNAMICS

The pharmacological effects of anticholinesterase drugs are predictable and reflect the accumulation of acetylcholine at muscarinic and nicotinic

cholinergic receptor sites. Muscarinic cholinergic effects, such as bradycardia, salivation, miosis, and hyperperistalsis are evoked by lower concentration of acetylcholine than are required for the production of effects at autonomic ganglia and the neuromuscular junction.

Cardiovascular effects

The cardiovascular effects of anticholinesterase drugs reflect the effects of accumulated acetylcholine at the heart (vagal effects), blood vessels, autonomic ganglia, and postganglinonic cholinergic nerve endings. Bradycardia and/or bradyarrythmias such as nodal and ventricular escape beats and asystole may occur. Bradycardia most likely reflects slowing of the conduction of cardiac impulses through the atrioventricular node. Decreases in systemic blood pressure that may accompany the accumulation of acetylcholine presumably reflect the decrease in systemic vascular resistance, although the coronary and pulmonary circulations may manifest an opposite response.

Gastrointestinal and genitourinary tract

Neostigmine enhances gastric fluid secretion by parietal cells and increases the motility of the entire gastrointestinal tract, particularly the large intestine. Neostigmine may increase the incidence of postoperative nausea and vomiting even when administered with atropine. The lower portion of the oesophagus is stimulated by neostigmine, resulting in a beneficial increase in

tone and peristalsis in patients with achalasia.

Salivary gland

Neostigmine augments production of secretory glands that are innervated by post-ganglionic cholinergic fibres. Such glands include the bronchial, lacrimal, sweat, salivary, gastric, intestinal and pancreatic glands.

Smooth muscle

Smooth muscle fibres of the bronchioles and ureters are contracted. Cholinergic stimulation results in bronchoconstrictron and anticholinesterase drugs have the potential to increase the airway resistance.

Eye

Miosis, inability to focus for near vision and a decrease in intraocular pressure occurs due to muscarinic actions.

CLINICAL USES OF NEOSTIGMINE

The principal clinical uses are:

1. Antagonist assisted reversal of neuromuscular blockade.
2. Treatment of myasthenia gravis
3. Postoperative analgesia – Intrathecal administration of neostigmine inhibits the metabolism of acetylcholine-released form the spinal cord.

Acetylcholine is one of more than 25 neurotransmitters that participate in spinal cord modulation of pain procession. In this regard, intrathecal and epidural neostigmine produce postoperative analgesia without producing ventilatory depression, characteristic of neuraxial opioids, although nausea is common.

Neurotoxicity does not accompany intrathecal or epidural administration of commercially available neostigmine preparations containing paraben preservatives (Eisenach et al 1997).

ASSESSMENT OF PAIN

Pain is a combination of severe discomfort, fear, autonomic changes, reflex activity and suffering. The intensity of pain can be measured in two ways:

1. Assessment by observers
2. Self reporting

In children, both these methods are used and in adults, the self-reporting method is most commonly used.

Assessment by observers

In children, the most commonly used scoring systems include

1. The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)
2. Pediatric objective pain scale

The arterial blood pressure, crying, movement, agitation and posture are taken for scoring in these two systems.

Self – reporting methods

These are most commonly used in adult patients and depend on the information given by the person in pain.

They are:

1. Visual Analogue Pain Scale
2. Henry Prince Pain Scale
3. CPR Pain Scoring
4. Facial Rating Scale
5. MC Gill Pain Questionnaire (MPQ)

In the present study, the Visual Analogue Pain Scale was used and hence it is discussed in detail here.

VISUAL ANALOGUE PAIN SCALE (VAS)

VAS provides simple, efficient and minimally intrusive method of assessment of pain intensity, which has been used widely in clinical and research settings where a quick assessment of pain is required and to which a numerical value can be assigned.

The most common VAS consists of a 10cm horizontal (Huskisscon 1983) or a vertical (Sriwatanakul et al 1983) line with the two endpoints labeled 'no pain' and 'worst pain ever'. The patient is required to place a mark on the 10cm line at a point with corresponds to the level of pain intensity he or she presently feels. The distance in centimeters from the lower end of the VAS to the patient's mark is used as a numerical index of the severity of pain.

Advantages of VAS

1. Its easiness.
2. Minimal intrusiveness
3. Provided that adequately clear instructions are given to the patient, its conceptual simplicity.

Disadvantages of VAS

1. It assumes that pain is a unidimensional experience.
2. It eliminates the possibility that each pain has unique qualities.

VAPS – Quality of Analgesia

0.1 Excellent

2.4 Good

5.6 Fair

7.8 Slight

9-10 No relief

Duration of analgesia

Duration of analgesia was defined as that period from the time of giving the epidural analgesia, till the patient's first requirement of systemic analgesics due to slight pain at rest. Supplementary analgesia was given when the pain score was more than 5 in the VAS.

REVIEW OF LITERATURE

1. Hartwig P et al and Gillberg P et al studied the effects of intrathecal acetylcholinesterase inhibitors and muscarinic receptor agonists in pain threshold in rats. There is now substantial evidence that acetylcholinesterase inhibitors and muscarinic receptor agonists increase the pain threshold after both systemic and spinal administration. In rats, physostigmine gave a significant dose-dependent increase in latency times in the tail immersion test following intrathecal administration. The effect was antagonized with atropine. Neostigmine gave more prolonged latencies as did the muscarinic receptor agonist carbachol. Spinal cholinergic pathways for antinociception interacted with the spinal opioid and adrenergic nerve tracts. No cross – tolerance to the selective alpha 2-adrenoreceptor agonist guanfacine or to morphine was seen in rats tolerant of spinal carbachol antinociception. The mechanism of spinal cholinergic antinociception is not known but a muscarinic interneuron may explain the interactions with other neurotransmitters.

2. Baba H, Okamoto M and Kohno T studied the muscarinic facilitation of GABA release in substantia gelatinosa of the rat spinal dorsal horn. Blind patch clamp recording were made form substantia gelatinosa (SG) neurons in the adult rat spinal cord slice to study the mechanisms of cholinergic modulation of GABAergic inhibition. In the majority of SG neurons tested,

carbachol (10μG) increased the frequency (677% of control) of spontaneous GABAergic Inhibitory Post Synaptic Currents (IPSCs). The effect of carbachol on spontaneous IPSCs was mimicked by neostigmine, suggesting that GABAergic interneurones are under tonic regulation by cholinergic systems. All the effects of carbachol and neostigmine were antagonized by atropine, while pirenzepine (100 nM), methoctramine (1μg) and hexahydrosiladifenidol hydrochloride, p-fluoroanalog (100nM) had no effect. Focal stimulation of deep dorsal horn, but not dorsolateral funiculus, evoked a similar increase in IPSC frequency to that evoked by carbachol and neostigmine. They have suggested that GABAergic interneurones possess muscarinic receptors on both axon terminals and somatodendritic sites, that the activation of these receptors increases the excitability of inhibitory interneurones and enhance GABA release in SG and that the GABAergic inhibitory system is further controlled by cholinergic neurons located in the deep dorsal horn. These effects may be responsible for the antinociceptive action produced by the intrathecal administration of muscarinic agonists and acetylcholinesterase inhibitors.

3. Tan PH, Chai YY and Lo Y compared the postoperative analgesic efficacy and safety of intrathecal (IT) neostigmine and IT morphine in patients undergoing total knee replacement under spinal anesthesia. Sixty patients scheduled for elective total knee replacement under spinal anesthesia were randomly divided into three equal groups who received IT 0.5% hyperbaric

bupivacaine 15mg with either normal saline 0.5 ml, neostigmine 50μg or morphine 300 μg. Results: There was no significant difference in maximal level of sensory block among the three groups. The morphine group had a later onset of post surgical pain and longer time to first rescue analgesics than the neostigmine group (P <0.05). Overall 24-hr VAS pain scores were significantly higher in the saline group Vs the morphine and neostigmine groups (P <0.05). Motor block lasted significantly longer in the neostigmine group than in the morphine and saline groups (P <0.05). The incidence of adverse effects was similar in the neostigmine and morphine groups except for pruritis (70%) occurring more frequently in the morphine group than in the neostigmine and saline group (0%; P <0.05). CONCLUSIONS: IT neostigmine 50 microgram produced postoperative analgesia lasting about seven hours with fewer side effects and better satisfaction rating than IT morphine 300μg.

4. Gurun Ms. Et al Leinbach R et al conducted studies on the safety of glucose and paraben-containing neostigmine for intrathecal administration. Initial toxicity testing of neostigmine for intrathecal (IT) injection was performed with preservative – free isobaric solution, yet currently available formulations contain the preservatives methyl and propylparaben and are usually mixed with glucose to yield hyperbaric solutions. Since it has been proposed that preservative and hyperbaricity increase the risk of neurotoxicity after IT injection, they examined the safety of chronically administered IT

neostigmine containing these additives in sheep and rats. Spinal cord histologic examination in both species revealed fibrosis and inflammation secondary to the catheter without evidence of neuronal damage. These studies support the safety of paraben- and glucose containing IT neostigmine.

5. Lauretti GR, de Oliveira R, Reis MP, Juliao MC, Pereira NL conducted a study to define the analgesic effectiveness of epidural neostigmine co administered with lignocaine and side effects in patients after minor orthopedic procedures. After 0.05-0.1 mg/kg intravenous midazolam premedication, patients were randomized into four groups to receive 20 mg intrathecal bupivacaine plus epidural lignocaine (85mg) with saline (control group)); 1 microgram/kg epidural neostigmine (1microgram group); 2 microgram/kg epidural neostigmine (2 microgram group); epidural neostigmine 4 microgram/kg (4 microgram group). Results: The visual analog scale score at first rescue analgesic and the incidence of adverse effects were similar among groups ($P > 0.05$). The time (min ± SD) to first rescue analgesic was as follows: control group: 205 ± 48; 1-microgram group: 529 ± 314; 2-microgram group: 504 ± 284; 4-microgram group: 547 ± 263 ($P < 0.05$). The analgesic consumption (number of intramuscular diclofenac injections [mean, 25^{th} 75^{th} percentile]) in 24 h was as follows: control groups: 3 (3 or 4); 1-microgram group:1 (1 or 2); 2-microgram group : 2 (1 or 2); 4-microgram 2 (1 or 3)

($P < 0.05$). The 24-h pain visual analog scale score (cm ± SD) that represents the overall impression for the last 24 hour was as follows: control group: 5 ± 1-6; 1-microgram group 1.6 ± 1.8; 2-microgram group: 1.4 ± 1.6; 4-microgram group: 2.2 ± 1.9 ($P < 0.005$). The incidence of adverse effects was similar among groups ($P > 0.05$). They concluded that epidural neostigmine (1,2 or 4 microgram / kg) in lignocaine produced dose – independent analgesic effect (approximately 8h) compared to the control group (approximately 3.5 h) and a reduction in postoperative rescue analgesic consumption without increasing the incidence of adverse effects.

6. Alpha 2-Adrenergic agonists are thought to produce analgesia, in part, by activating spinal acetylcholine release. **Hood et al and Mallak et al** studied the interaction between intrathecal neostigmine and epidural clonidine for analgesia and side effects in humans. The combination of neostigmine and clonidine resulted in an additive enhancement of analgesia, but no enhancement of each drug's side effects, and a reduction in clonidine induced hypotension. Neostigmine injected into subjects in the lateral position diminished clonidine – induced reductions in blood pressure and plasma norepinephrine. Hence, their results support enhancement of alpha 2- adrenergic analgesia by intrathecal neostigmine, but do not demonstrate synergy, as observed in animals. Lack of enhancement of side effects suggests this combination may be clinically useful.

7. Nakayama et al evaluated the effects of epidurally administered neostigmine on pain after abdominal hysterectomy. 45 ASA I status adult patients received general and epidural anaesthetic. At the end of surgery, they received epidural bupivacaine 10mg with saline (n=15), 5 microgram/kg neostigmine or 10 microgram / kg neostigmine. If patient wants additional pain relief, 50mg diclofenac suppository was given. The time to first diclofenac administration was significantly longer ($P < 0.05$) in the 10 microgram/kg group than in the control group or 5-microgram / kg groups. They concluded that epidural neostigmine 10 microgram/kg with bupivacaine provides a longer duration of analgesia than does bupivacaine with or without 5 microgram/kg after abdominal hysterectomy.

8. Lauretti GR, de Oliveira R et al postoperative analgesia by intra – articular neostigmine 1 microgram/kg or 500 micrograms or epidural neostigmine 1 microgram/kg. They concluded that although peripheral neostigmine 1 microgram/kg did not result in postoperative analgesia, the same dose applied epidurally results in over 5 hours of analgesia similar to five-fold dose applied peripherally. The results suggest that epidural neostigmine has a greater analgesic efficacy than peripherally applied neostigmine.

9. Owen MD, Ozsarac O, Sahin S, Uckunkaya N, Kaplan N, Magunaci studied the addition of low dose clonidine and neostigmine on the duration of analgesia for labour. Forty – five healthy parturients in active labor

were randomized to receive a 2 ml intrathecal dose of one of the following dextrose – containing solutions using the combined spinal epidural technique (1) bupivacaine 2.5mg and fentanyl 125 microgram (BF) l (2) BF plus clonidine 30 microgram (BFC); or (3) BFC plus neostigmine 10 microgram (BFCN). Pain scores, block characteristics, maternal vital signs, Apgar scores, maternal satisfaction, and side effects were similar among groups except for nausea, which was significantly greater in the BFCN group ($P < 0.05$ as compared with BFC). The addition of clonidine and neostigmine significantly increased the duration of analgesia form intrathecal bupivacaine – fentanyl during labour, but neostigmine caused more nausea. Although serious side effects were not observed in this study, safety must be further addressed before the routine use of multiple intrathecal drugs is advocated.

10. Tan P-H et al studied the efficacy and safety of intrathecal neostigmine for the relief of pain for patients having undergone inguinal herniorrhaphy. Sixty men undergoing elective inguinal herniorrhaphy with spinal anaesthesia were randomly allocated into three groups of 20 each, group I received intrathecal tetracaine 15 mg, group II received intrathecal tetracaine 15mg with neostigmine 50 micrograms and group III received intrathecal tetracaine 15mg with neostigmine 100 micrograms. Onset of anaesthesia was significantly faster for groups II and III; motor block was greatly prolonged for group III patients with an average of 6.4hr, compared with 4.1hr for group II.

Group III patients also showed later onset of post surgical pain; lower overall 24hr Visual Analogue Score and prolonged time to first rescue analgesia than did group II patients. They concluded that intrathecal neostigmine at 50 micrograms or 100 micrograms enhanced that onset of tetracaine anaesthesia and provided analgesia for 6-9h although, increased incidences of prolonged motor blockade and nausea or vomiting were noted.

11. Hood DD, Eisenach JC, Tuttle R studied the safety on intrathecal neostigmine methyl sulfate in humans. 28 healthy volunteers were divided into two groups; the first 14 volunteers received neostigmine 500-750 microgram caused severe nausea and vomiting. Neostigmine by either method of administration reduces visual analogue pain scores to immersion of the foot in ice water. The study concluded that no dangerous side effects occurred.

12. Kirdemit P et al compared the analgesia and side effects of preemptively used epidural ketamine + bupivacaine, neostigmine + bupivacaine and bupivacaine alone on postoperative analgesia after major abdominal surgery. 30 ASA I/II/III patients undergoing general anaesthesia were selected; group N received 0.5mg neostigmine and bupivacaine 25mg epidurally, group B received 1ml saline and 25mg bupivacaine epidurally and group K received ketamine 50mg and bupivacaine 25mg epidurally 30 minutes before operation. All underwent general anaesthesia with thiopentone and vecuronium induction, and were maintained with isoflurane and vecuronium. In group N Visual

Analogue Score and total postoperative opioid consumption was significant lower than in groups K and B they concluded that pre-emptive neostigmine could be a good choice for post operative analgesia.

13. Lauretti G R, Hood DD et al reported a multicentric, placebo-controlled trial, which investigated the effects of 25-75 microgram intrathecal neostigmine on analgesia and blood pressure in women undergoing vaginal hysterectomy. 92 women scheduled for vaginal hysterectomy were randomized to receive an intrathecal injection of 2ml of bupivacaine 0.75% in dextrose with either 1ml saline or 25,50, or 75 μg neostigmine. Pain, nausea, haemodynamic profile and postoperative morphine use was assessed. The study showed that morphine use was reduced by all doses of neostigmine; incidence of nausea was greater in patients receiving neostigmine (61%) than in those who received saline placebo. No significant change in haemodynamic status was noted in all groups. The study concluded that analgesia from intrathecal neostigmine may occur at doses less than 50 μg and that neostigmine does not reduce spinal bupivacaine induced hypotension.

14. Lauretti GR, Mattos AL, Reis MP, Prado WA studied the effect of intrathecal neostigmine for postoperative analgesia after orthopedic surgery. 60 ASA physical status I and II unpremedicated patients undergoing orthopedic surgery (tibial or ankle reconstruction) were given spinal anesthesia in the sitting position, L3-L4 interspace, and 4 ml volume, injected at a rate of 1

ml/10sec. The control group – (CG) received 15mg hyperbaric bupivacaine 0.5% plus saline. The 25 μg neostigmine group (25NG) received 15mg hyperbaric bupivacaine plus 25μg neostigmine; the 50 μg neostigmine group (50NG) received 15 mg hyperbaric bupivacaine plus 50 micrograms neostigmine; and the 100 μg neostigmine group (100NG) received 15mg hyperbaric bupivacaine plus 100 μg neostigmine. Times to first rescue analgesics, analgesia, and adverse effects at constant intervals were assessed using the 10cm visual analog scale (VAS). Intrathecal neostigmine produced a dose-independent reduction in the postoperative rescue analgesic consumption ($p<0.0001$). The time to first rescue analgesics was similar among groups ($p<0.05$), and the overall 24-hour VAS pain scores were lowest for patients who had spinal neostigmine ($p<0.02$). The 100NG group had the highest incidence of postoperative nausea and vomiting of all the groups ($p<0.05$). The study concluded intrathecal neostigmine produced a dose-independent analgesia and a dose dependent incidence of adverse effects with the doses studied.

15. S. P. Chittora et al studied the effect of neostigmine as an additive to lignocaine for postoperative analgesia in intrathecal and epidural anaesthesia. Neostigmine 50 microgram added to 5% lignocaine given intrathecally prolonged duration of analgesia from 123.3 ± 14.8 minutes in lignocaine group to 368.1 ± 145.4 minutes in lignocaine + neostigmine. Nausea in 25%, vomiting

in 20%, hypotension and sweating in 5% of total cases was observed. Nausea and vomiting were severe in neostigmine group compare to plain lignocaine group. The neostigmine 100 microgram epidurally provided comparable prolongation of analgesia (355 ± 105 minutes) to intrathecal neostigmine group (368.1 ± 145.4)

16. De-Rosa et al have shown significant increase in postoperative analgesia from 85 ± 10 minutes to 270 ± 43 minute in bupivacaine – neostigmine group compared to bupivacaine alone.

17. Klamt et al found that spinal neostigmine with bupivacaine as effective as morphine and significantly prolonged the duration of analgesia compared with saline. It was 4.5 ± 1, 15.3 ± 7.1 and 10.7 ± 4.3 hours for saline, morphine (100 microgram) and neostigmine (100 microgram) groups respectively.

18. Rudra A et al found that caudal administration of bupivacaine with the addition of neostigmine resulted in superior analgesia compared with bupivacaine alone. Requirement of initial analgesic to provide pain relief in the postoperative period was after 7.6 ± 5.4 hours of surgery in 40 children belonging to bupivacaine group. However, the requirement of initial pain relieving agent was after 19.0 ± 4.2 hours of surgery in 40 children, those who received caudal bupivacaine plus neostigmine.

19. Abdulatif M, Turan A, et al in their studies with 2 microgram/kg of neostigmine have not mentioned any behavioral or histological evidence of neurotoxicity from epidural administration of neostigmine with methyl and propylparaben as preservatives in a glucose containing solution.

METHODOLOGY

Study Design: **Double blind randomized clinical trial**

This prospective clinical study was conducted at Government Rajaji Hospital. Madurai, after obtaining Ethical Committee Clearance, in 50 patients. Informed consent was obtained from each patient after explaining the procedure in detail.

The patients posted for elective lower abdominal surgeries were chosen at random. ASA grade I patients of both sex with, age ranging from 18 to 75 years were included in the study. Pregnant and lactating females, patients with spinal deformities, local skin sepsis, bleeding disorders and psychiatric illness were excluded from the study.

Pre-anaesthetic evaluation

A complete physical examination was done to detect any abnormality in heart, lung, abdomen and central nervous system. Assessment was also done to exclude any local disease, which may interfere with anaesthesia.

Routine biochemical, haematological investigations, ECG, and chest X-ray were taken. Baseline measurements of respiratory rate, breath holding time and SpO_2 were done. Patients were explained about the 10-point visual analog scale.

The 50 patients were allocated into 2 groups

- Group B receiving **20 ml of 0.5% bupivacaine** with adrenaline 5microgram/ml + 1 ml of normal saline and
- Group BN receiving **20 ml of 0.5% bupivacaine** with adrenaline 5 microgram/ml + **100 microgram of neostigmine** in 1 ml of normal saline.

Anaesthetic Technique

No premedication was given to these patients.

The following resuscitative measures were kept ready before administering epidural anaesthesia.

Boyle's machine with oxygen supply.

Laryngoscope and appropriate size endotracheal tubes.

Suction apparatus

Vasopressors and other emergency drugs.

Contents of the epidural tray were: sponge holding forceps, sterile gauze pieces, bowl with antiseptic solutions, sterile towels, 24 gauge needle and 5 ml syringe, 16 gauge Tuohy needle, 16 gauge epidural catheter, 10 ml glass syringe with freely moving piston, 2% lignocaine vial, 0.5% bupivacaine vial injection adrenaline, injection neostigmine.

After positioning the patients in the right lateral decubitus position, a 16 gauge Tuohy needle was used to perform the midline epidural block in L_2-L_3 or L_3-L_4 space, with " loss of resistance to air " technique being used to identify

the epidural space. A 16 gauge epidural catheter was inserted upto 5 cms length, directed cephalad and fixed in place. Aspiration was done to rule out subarachanoid or intravascular placement of the catheter. A test dose of 2 ml of 1.5%lignocaine with 5μg/ml of adrenaline was given through the catheter. Later, the total dose of the local anaesthetic was given through the catheter and the patient was placed in supine position.

The level of sensory blockade was assessed every 2 minutes. The time taken for the onset of sensory block at T_{10} and the time taken for the maximum level of sensory block was noted down. The time taken for onset of grade 3 motor block was also noted.

The pulse rate, blood pressure and respiratory rate were monitored every 5 minutes, throughout the surgery. Hypotension was defined as ≥20% decrease in systolic blood pressure from the baseline value and bradycardia was defined as pulse rate ≤60/min. Treatment plan for hypotension was, rushing of intravenous fluids and administration of injection ephedrine 6mg intravenous boluses. Treatment plan for bradycardia was administration of injection atropine sulphate intravenously. Continuous SpO_2 monitoring was done. The patients were also observed for other complications of neostigmine like nausea, vomiting bradycardia, drowsiness, sedation, increased secretions and intestinal cramps. The two-segment regression time and the duration of surgery was noted.

Post Operative Monitoring

At the end of the surgery, the epidural catheter was removed under, aseptic precautions and a seal of tincture benzoin was applied. Patients were observed in the recovery room for the next 1 hour and sent to the postoperative ward where, vital parameters like pulse rate, blood pressure, respiratory rate, SpO_2 were recorded every 30 minutes for the next 6 hours and hourly thereafter till the patient's first requirement of systemic analgesic medication. Patients were also observed for complications like bradycardia, vomiting, hypotension, sedation, bronchoconstriction, respiratory depression or abdominal cramps during the surgery and in the postoperative period.

Although preservative free neostigmine is not associated with neurotoxicity it is no longer marketed. Many studies have established the absence of any behavioral or histological evidence of neurotoxicity from epidural administration of neostigmine with methyl and propyl paraben as preservatives. Therefore, we believed that the dose of neostigmine with methyl paraben as preservative used in our study would not result in any neurotoxicity. Neurological sequalae, including persistant paraesthesia, sensory or motor deficit and bowel or bladder dysfunction were reviewed in the subsequent days and outpatient followup.

The level of consciousness was assessed every 30 minutes and graded according to the sedation score (Brian and Ready).

0 – fully awake

1 – normal sleep

2 – drowsy, arousable on touch

3 – drowsy, arousable to painful stimuli

4 – somnolent.

Duration of analgesia

Duration of analgesia was defined as that period from the time of giving the epidural anaesthesia till the patient's first requirement of systemic analgesic medication. In this study, patients with VAS > 5 were given systemic supplementary analgesics.

VAS Scoring

Patients were asked to point the intensity of pain on the 10-point visual analog scale of pain. The first VAS score was noted and the time at which patients request additional systemic analgesics was noted.

RESULTS

The statistical analysis of the data is presented as **mean ± standard deviation.** The two groups were compared by **student 't' test** and $p<0.05$ was considered as significant.

OBSERVATIONS AND RESULTS

In the present study, patients who underwent lower abdominal surgeries

were divided into two groups.

Group B – Receiving **20ml of 0.5% Bupivacaine** with 5μg/ml of adrenaline + 1ml of normal saline.

Group BN – Receiving **20 ml of 0.5% Bupivacaine** with 5μg/ml of adrenaline + **100 μg of neostigmine** in 1ml of normal saline.

Patients in both groups were comparable in age, sex and weight distribution. All were ASA grade I patients.

None of the patients had narcotic premedication or intra-operative analgesic supplementation.

Age Distribution

The minimum and maximum age in group B was 18 and 74 years respectively. The minimum and maximum age in group BN was 18 and 65 years respectively. The mean age of patients (in years), in group B was 46.32 ± 13.51 and group BN patients was 42.24 ± 13.22. 'p' value – 0.282 ($p > 0.05$, which is not statistically significant). The details are given in Table – 2.

Weight distribution

The minimum and maximum weight in group B was 40 and 70 kg respectively. The minimum and maximum weight in group BN was 40 and 80kg respectively. The mean weight of the patients (in kilograms) in group B was 51 ± 6.82 and in group BN was 53.08 ± 8.71. 'p' value – 0.346 ($p > 0.05$, which is not statistically significant). The details are given in Table -2.

Time of onset of block at T_{10}

In both groups, the minimum and maximum time taken for onset of sensory blockade at T_{10} was 5 minutes and 10 minutes respectively, with a mean of 7.28 ± 1.30 minutes in group B and 6.56 ± 1.44 in group BN. 'p' value- 0.073. ($p > 0.05$, which is not statistically significant). The details are provided in Table – 3.

Time for maximum level of sensory block

The time for the maximum level of sensory block in group B was between 8 - 18 minutes with mean of 13.28 ± 2.22 minutes and in group BN was between 10 – 20 minutes with a mean of 14.16 ± 2.71 minutes. 'p' value – 0.158 ($p > 0.05$, which is not statistically significant). The details are provided in Table – 3.

Maximum level of sensory block

In both groups the maximum level of sensory block attained was between $T_4 – T_6$ with a mean of $T_{4.72±0.93}$ in group B and $T_{4.32±0.74}$ in group BN ($p > 0.05$, which is not statistically significant).

Time for Grade 3 motor block

In group B the grade 3 motor block was achieved with a mean of 16.6 ± 4.04 minutes and in group BN it was with the mean of 17.96 ± 3.8

minutes. ‘p’ value – 0.24 ($p > 0.05$, which is not statistically significant). The details are provided in Table – 3.

Two segment regression time

In group B the two segment regression time was in the range of 80 minutes to 135 minutes with a mean of 111.8 ± 12.9 minutes and in group BN it was in the range of 90 minutes to 180 minutes with a mean of 123.6 ± 20.43 minutes. **‘p’ value – 0.035 ($p < 0.05$, which is statistically significant).** The details are shown in Table – 4.

Duration of surgery

In group B, the mean duration of surgery was 111 ± 19.14 minutes and group BN it was 117.8 ± 31.16 minutes. ‘p’ value – 0.413 ($p > 0.05$, which is not statistically significant). The details are shown in Table – 4.

DURATION OF POSTOPERATIVE ANALGESIA

In group B, the minimum duration of analgesia was 240 minutes and maximum duration was 330 minutes with a mean of 286.8 ± 23.44 minutes; standard error of 4.68 minutes and group BN the minimum duration of analgesia was 360 minutes and maximum duration was 720 minutes with a mean of 515.8 ± 89.69 minutes; standard error 17.93 minutes. **‘p’ value – 0.0001 ($p << 0.05$ which is statistically highly significant).** The 95% confidence interval for group B was 277.12 to 296.47 minutes and in group BN it was 478.77 to 552.82 minutes. The details are represented in Table – 5.

Vitals

Oxygen saturation which was measured by pulse-oximetry was maintained above 97% in all patients in both the groups.

Respiratory rate was > 10/min in all of the patients.

Heart rate and **mean arterial pressure** was comparable in both groups.

Complications

Hypotension occurred intra-operatively in 3 patients in group B (12%) and 2 patients in group BN (8%), $p > 0.05$, which is not statistically significant.

Vomiting occurred in the recovery room in 2 patients in group B (8%) and 4 patients in group BN (16%), $p > 0.05$, which is not statistically significant.

No patients developed **bradycardia**, which was taken as a heart rate less than 60/min.

No patients developed complications like, bronchoconstriction sedation, respiratory depression or abdominal cramps during and after the surgery, in both the groups.

DISCUSSION

In the recent years, many drugs have been combined with local anesthetics in the epidural route for providing postoperative pain relief. Opioids have been successfully used for this purpose but they have their own side effects like nausea, vomiting, respiratory depression and pruritis.

Hence many adjuvants like neostigmine, ketamine and clonidine are being used in the epidural route in combination with local anaesthetics for providing postoperative analgesia. The present study was to evaluate the efficacy of neostigmine, along with bupivacaine in the epidural route for postoperative analgesia.

Mechanism of action of neostigmine in the spinal cord

Baba et al and Kohno et al studied the muscarinic facilitation of GABA release in substantia gelatinosa of the rat spinal dorsal horn. They concluded that GABAergic interneurones possess muscarinic receptors on both axon terminals and somatodendritic sites, that the activation of these receptors increases the excitability of inhibitory interneurones and enhances GABA release in the substantia gelatinosa and that the GABAergic inhibitory system is further controlled by cholinergic neurons located in the deep dorsal horn. These

effects may be responsible for the antinociceptive action produced by the intrathecal administration of muscarinic agonists and acetylcholinesterase inhibitors.

Smith et al has concluded from his studies that there is a role of endogenous spinal acetylcholine in pain modification and suggested an interaction with substance P neurons of the dorsal spinal cord.

Hood et al proposed that α_2 adrenergic agonists are thought to produce analgesia, in part, by activating spinal acetylcholine release.

Hartwig et al postulated that spinal cholinergic pathways for antinociception interacted with the spinal opioid and adrenergic nerve tracts. There is now substantial evidence that acetylcholinesterase inhibitors and muscarinic receptor agonists increase the pain threshold after both systemic and spinal administration. The mechanism of spinal cholinergic antinociception is not known but a muscarinic interneuron may explain the interactions with other neurotransmitters.

Eisenach et al proposed that muscarinic receptors are concentrated in the superficial layers of the dorsal horn of the spinal cord, an area of noxious sensory processing, and these reflect innervation primarily from cholinergic neurons with cell bodies deep in the neck of the dorsal horn. Spinal injection of cholinergic agonist results in analgesia that primary affects muscarinic receptor activation.

Seybold VS et al studied the existence of muscarinic receptors, both M_1 and M_2, in laminae II and III of the spinal cord autoradiographically.

Tuttle et al Proposed analgesia by cholinesterase inhibitors depend on degree of spinal cholinergic tone in some species and the tonic spinal cholinergic activity in normal human is adequate for neostigmine to produce meaningful analgesia alone.

Rudra A. et al has concluded that Neostigmine an anticholinesterase inhibitor may cause an accumulation of ACh at the muscarinic receptors in the dorsal horn when entered into CSF. Thus, increased spinal levels of ACh may augment antinociceptive effects as a result of axonal conduction block from epidural bupivacaine. A potent advantage of central neuraxial neostigmine is that, it may counteract local anaesthetic induced hypotension by inhibitory effect on the sympathetic nerve activity. In the current study, the observed perioperative haemodynamic stability with the use of bupivacaine plus neostigmine mixture supports this contention.

COMPARISION OF RESULTS

There were no significant differences in the time taken for the onset of sensory block at T10, time taken for grade 3 motor block, the maximal level of sensory block and the time taken to achieve maximum level of sensory block, between the two groups.

Hence, neostigmine had no effect on the speed of onset of sensory block, which is similar to the findings of Bone H.G et al. But, this is contrary to the findings of Tan P.H et al who showed that intrathecal neostigmine produces faster onset of anaesthesia. This may be because, they had used 50µg neostigmine with 3cc of 0.5% bupivacaine intrathecally but, in our present study 100µg of neostigmine with 20cc of 0.5% bupivacaine epidurally. The larger volume of the drug used for epidural administration has diluted the 100µg of neostigmine used. This and the dural cuff must have acted as barriers, to the diffusion of neostigmine into the spinal cord and spinal nerve roots

Also, neostigmine had no effect on the speed of onset of motor block.

The two segment regression time was delayed in the neostigmine group by an average of 11.8 ± 7.53 minutes, which was clinically significant 'p'value-0.035. $p < 0.05$,which is statistically significant.

The incidence of hypotension in the neostigmine group was comparable to the control group. Vomiting occurred in 16% of patients in neostigmine group compared to 8% in control group but it was not statistically significant.

The duration of postoperative analgesia was enhanced significantly, when neostigmine was added to bupivacaine in the epidural space. The mean duration of postoperative analgesia in the bupivacaine group was 286.8 ± 23.44 minutes and in the bupivacaine + neostigmine group was 515.8 ± 89.69 minutes. The duration of post operative analgesia in neostigmine group is prolonged by 229 ± 66.25 minutes which was clinically significant. The p value is 0.0001, p <<< 0.5, which is statistically highly significant.

The results correlate favourably with the studies conducted by, **Lauretti GR et al and de Oliveira R et al** who studied the effect of three different doses of epidural neostigmine co-administered with bupivacaine for postoperative analgesia, **Nakayama et al** who studied the analgesic effect of epidural neostigmine after abdominal hysterectomy, **Lauretti GR et al and Perez MV et al** who studied the postoperative analgesia of epidural neostigmine following knee surgery and **Rudra A et al** who studied the analgesic effect of caudal neostigmine with bupivacaine for post-op analgesia and have concluded that the **administration of neostigmine in the epidural space along with a local anaesthetic produces good postoperative analgesia.**

CONCLUSION

The study was done to evaluate the efficacy of epidurally administered neostigmine along with bupivacaine for postoperative pain relief in lower abdominal surgeries and to evaluate the merits and demerits of neostigmine administered epidurally.

The conclusion is that **the epidural administration of neostigmine in the dose of 100 µg along with 0.5% bupivacaine with adrenaline 5 µg/ml prolongs the duration of postoperative analgesia significantly, with no serious side-effects** and does not have any effect on the time taken for the onset of sensory and motor blockade.

So, NEOSTIGMINE a commonly available drug could be safely used to provide effective post-operative pain relief for patients undergoing lower abdominal surgeries. Hence, NEOSTIGMINE would prove as a cost- effective adjuvant for local anaesthetics and will also prolong the duration of postoperative analgesia considerably and significantly, without producing serious side effects.

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PROFORMA

DEPARTMENT OF ANESTHESIOLOGY

MADURAI MEDICAL COLLEGE

MADURAI

Comparative evaluation of epidural bupivacaine with neostigmine and epidural bupivacaine alone in lower abdominal surgeries for postoperative analgesia

Name:	Age/Sex:	Address:	I.P.No:
Diagnosis:	Surgery:	D.O.S.	Unit:
Anaesthesiologist:		Surgeon:	

Pre anaesthetic assessment		**Pre operative investigations**	
General condition	:	Urine-Albumin, Sugar & Deposits:	
Weight	:	Hb%	:
CVS	:	Bleeding Time	:
RS	:	Clotting Time	:
Pulse	:	Blood Urea	:
BP	:	Blood Sugar	:
Spines	:	Serum Creatinine	:
Airway	:	Blood Grouping	:
ASA status	:	Chest X ray	:
		ECG	:

Premedication:

Drug: Dose: Route: Time:

Technique of Anaesthesia: Position:

Space: Approach: Needle: Catheter

Drugs administered: Bupivacaine Neostigmine Volume of drug:

Time of Administration: Time of onset of block at T_{10}:

Maximum level of sensory block: Time for grade 3 motor block:

Time to attain maximum level of sensory block:

Two segment regression time: Duration of surgery:

INTRA OPERATIVE MONITORING

Time (in minutes)	**Level of block**	**Pulse rate**	**Blood pressure**	**Respiratory rate**	**SPO_2**	**Level of consciousness**	**Complications (if any)**

POSTOPERATIVE MONITORING

Time (in hours)	**VAS**	**Pulse rate**	**Blood pressure**	**Respiratory rate**	**Level of consciousness**	**Complications (if any)**

Duration of analgesia (in minutes):

COMPLICATIONS (if any)

Nausea

Vomiting

Bradycardia

Hypertension

Sedation

Abdominal cramps

Increased secretions